Clinical trial results:
A Randomized, Multicenter, Open-Label Phase II Study of RO5083945 in Combination with FOLFIRI versus FOLFIRI plus Cetuximab or FOLFIRI Alone as Second Line Treatment in Patients with KRAS Wild-Type or Mutant Metastatic Colorectal Cancer

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2010-022983-11
Trial protocol	GB FR BE DE ES IT
Global end of trial date	19 December 2013

Results information

Result version number	v2 (current)
This version publication date	03 March 2016
First version publication date	08 August 2015
Version creation reason	• Correction of full data set Quality check of the data entered before the system became unavailable

Trial information

Trial identification

Sponsor protocol code	BP25438

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01326000
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline , F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was randomized, multicenter, open-label, Phase II study of RO5083945 in combination with FOLFIRI versus FOLFIRI plus cetuximab or FOLFIRI alone.
The primary objectives were as follows:
1. To gather preliminary evidence of superior activity of RO5083945 added to FOLFIRI versus FOLFIRI + cetuximab in terms of progression free survival (PFS) in participants with Kirsten sarcoma rat virus homology (KRAS) wild-type (WT) colorectal cancer (CRC).
2.To gather preliminary evidence of superior activity of RO5083945 added to FOLFIRI versus FOLFIRI alone in terms of PFS in participants with KRAS mutant CRC.

Protection of trial subjects:

The investigator ensured that the study was performed in full conformance with the principles of "Declaration of Helsinki" and with the local laws and regulations where the trial was conducted. The study adhered to the principles outlined in "Guideline for Good Clinical Practice" International conference on Harmonization (ICH) Tripartite guideline and compliance with European Union (EU) Clinical Trial Directive (for studies conducted in EU) and adherence to the basic principles of “Good Clinical Practice” as outlined in the current version of 21 code of federal regulations (CFR(, subchapter D, part 312, “Responsibilities of Sponsors and Investigators”, part 50, “Protection of Human Patients”, and part 56, “Institutional Review Boards”, when conducted in United States.
A written informed consent is obtained from participants. The investigator or designee explained the trial so that the participants were completely free to refuse or withdraw the study at any point of time. Additional procurement of assent from legally incompetent persons and minors took place according to local laws and international best practice, as it applies to the specific case.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	28 April 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	10 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Spain: 45
Country: Number of subjects enrolled	United Kingdom: 37

Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	169
EEA total number of subjects	122

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	101
From 65 to 84 years	68
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eligibility screening form documenting the investigator's assessment of each participant with regard to inclusion and exclusion criteria was completed by investigator. Data generated from a fresh tumor biopsy (for determination of KRAS status and levels of epidermal growth factor receptor expression) were considered for inclusion of participants.

Period 1

Period 1 title	Started (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	KRAS Wild Type (Cetuximab + FOLFIRI)

Arm description:

Cetuximab: The first dose of cetuximab was 400 milligrams per square meter (mg/m2) body surface area for 120 minutes on Day 1 of Cycle 1 followed by weekly doses of 250 mg/m2 for 60 minutes as an intravenous (IV) infusion until disease progression, unacceptable toxicity, or withdrawal of consent.
FOLFIRI: FOLFIRI is a combination of irinotecan,5-fluorouracil (5-FU), and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46 to 48-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm type	Active comparator
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab 400 mg/m2 body surface area for 120 minutes on Day 1 of Cycle 1 followed by weekly doses of 250 mg/m2 for 60 minutes as an IV infusion.

Arm title	KRAS Wild Type (RO5083945 + FOLFIRI)

Arm description:

RO5083945: RO5083945 1400 mg administered as an IV infusion on Day 1 of Weeks 1 and 2, then once every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.
FOLFIRI: FOLFIRI is a combination of irinotecan, 5-FU, and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46 to 48-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm type	Experimental

Investigational medicinal product name	RO5083945
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

RO5083945 1400 mg IV administered on Day 1 of Weeks 1 and 2 and then once every 2 weeks.

Arm title	KRAS Mutant (FOLFIRI)

Arm description:

FOLFIRI: FOLFIRI is a combination of irinotecan, 5-FU, and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46 to 48-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm type	Standard of care

No investigational medicinal product assigned in this arm

Arm title	KRAS Mutant (RO5083945 + FOLFIRI)

Arm description:

RO5083945: RO5083945 1400 mg administered as an IV infusion on Day 1 of Weeks 1 and 2, then once every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.
FOLFIRI: FOLFIRI is a combination of irinotecan, 5-FU, and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46 to 48-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	RO5083945
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

RO5083945 1400 mg IV administered on Day 1 of Weeks 1 and 2 and then once every 2 weeks.

Number of subjects in period 1	KRAS Wild Type (Cetuximab + FOLFIRI)	KRAS Wild Type (RO5083945 + FOLFIRI)	KRAS Mutant (FOLFIRI)
Started	41	41	43
Completed	0	0	0
Not completed	41	41	43
Consent withdrawn by subject	-	2	-
Death	27	23	31
Unspecified	14	16	12

Number of subjects in period 1	KRAS Mutant (RO5083945 + FOLFIRI)
Started	44

Completed	0
Not completed	44
Consent withdrawn by subject	2
Death	33
Unspecified	9

Baseline characteristics

Reporting groups

Reporting group title	KRAS Wild Type (Cetuximab + FOLFIRI)

Reporting group description:

Cetuximab: The first dose of cetuximab was 400 milligrams per square meter (mg/m2) body surface area for 120 minutes on Day 1 of Cycle 1 followed by weekly doses of 250 mg/m2 for 60 minutes as an intravenous (IV) infusion until disease progression, unacceptable toxicity, or withdrawal of consent.
FOLFIRI: FOLFIRI is a combination of irinotecan,5-fluorouracil (5-FU), and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46 to 48-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Reporting group title	KRAS Wild Type (RO5083945 + FOLFIRI)

Reporting group description:

RO5083945: RO5083945 1400 mg administered as an IV infusion on Day 1 of Weeks 1 and 2, then once every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.
FOLFIRI: FOLFIRI is a combination of irinotecan, 5-FU, and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46 to 48-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Reporting group title	KRAS Mutant (FOLFIRI)

Reporting group description:

FOLFIRI: FOLFIRI is a combination of irinotecan, 5-FU, and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46 to 48-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Reporting group title	KRAS Mutant (RO5083945 + FOLFIRI)

Reporting group description:

RO5083945: RO5083945 1400 mg administered as an IV infusion on Day 1 of Weeks 1 and 2, then once every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.
FOLFIRI: FOLFIRI is a combination of irinotecan, 5-FU, and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46 to 48-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Reporting group values	KRAS Wild Type (Cetuximab + FOLFIRI)	KRAS Wild Type (RO5083945 + FOLFIRI)	KRAS Mutant (FOLFIRI)
Number of subjects	41	41	43
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.9	60	63.2
standard deviation	± 13	± 12.5	± 10.6

Gender categorical Units: Subjects			
Female	13	14	14
Male	28	27	29

Reporting group values	KRAS Mutant (RO5083945 + FOLFIRI)	Total	
Number of subjects	44	169	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.6		
standard deviation	± 12.1	-	
Gender categorical Units: Subjects			
Female	18	59	
Male	26	110	

End points

End points reporting groups

Reporting group title	KRAS Wild Type (Cetuximab + FOLFIRI)

Reporting group description:

Cetuximab: The first dose of cetuximab was 400 milligrams per square meter (mg/m2) body surface area for 120 minutes on Day 1 of Cycle 1 followed by weekly doses of 250 mg/m2 for 60 minutes as an intravenous (IV) infusion until disease progression, unacceptable toxicity, or withdrawal of consent.
FOLFIRI: FOLFIRI is a combination of irinotecan,5-fluorouracil (5-FU), and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46 to 48-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Reporting group title	KRAS Wild Type (RO5083945 + FOLFIRI)

Reporting group description:

RO5083945: RO5083945 1400 mg administered as an IV infusion on Day 1 of Weeks 1 and 2, then once every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.
FOLFIRI: FOLFIRI is a combination of irinotecan, 5-FU, and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46 to 48-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Reporting group title	KRAS Mutant (FOLFIRI)

Reporting group description:

FOLFIRI: FOLFIRI is a combination of irinotecan, 5-FU, and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46 to 48-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Reporting group title	KRAS Mutant (RO5083945 + FOLFIRI)

Reporting group description:

RO5083945: RO5083945 1400 mg administered as an IV infusion on Day 1 of Weeks 1 and 2, then once every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.
FOLFIRI: FOLFIRI is a combination of irinotecan, 5-FU, and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46 to 48-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Primary: Progression-Free Survival (PFS) in KRAS WT Participants

End point title	Progression-Free Survival (PFS) in KRAS WT Participants[1]

End point description:

PFS was defined as the time between randomization and date of first documented disease progression or death, whichever occurs first. Progressive disease (PD) is at least a 20% increase in the sum of diameter of target lesions, taking as reference the smallest on study including baseline. Participants who neither progressed nor died at the time of the clinical cut-off or who were lost to follow-up were censored at the date of the last tumor assessment showing no progression of disease either during the study or during follow-up. Participants with no post-baseline assessments were censored at the date of randomization. PFS was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version (v).1.1. criteria. Three participants each in the KRAS WT Cetuximab + FOLFIRI and RO5083945 were censored for PFS analysis.

Analysis population: Intent-to-Treat (ITT) population; All randomized participants.

End point type	Primary

End point timeframe:

Randomization up to clinical cutoff (20.9 months)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point reported statistics only on the KRAS WT participants.

End point values	KRAS Wild Type (Cetuximab + FOLFIRI)	KRAS Wild Type (RO5083945 + FOLFIRI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	41		
Units: Months				
median (confidence interval 95%)	6.1 (5.4 to 9.2)	7.3 (5.3 to 8.4)		

Statistical analyses

Statistical analysis title	PFS in KRAS Wild Type Participants
Comparison groups	KRAS Wild Type (Cetuximab + FOLFIRI) v KRAS Wild Type (RO5083945 + FOLFIRI)
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6249 [2]
Method	Log-Rank, stratified
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.86

Notes:

[2] - The three stratification factors included epidermal growth factor receptor (EGFR) expression, time to disease progression on first line treatment, and prior treatment with bevacizumab.

Primary: PFS in KRAS Mutant Participants

End point title	PFS in KRAS Mutant Participants[3]

End point description:

PFS was defined as the time between randomization and date of first documented disease progression or death, whichever occurs first. PD was at least a 20% increase in the sum of diameter of target lesions, taking as reference the smallest on study including baseline. Participants who neither progressed nor died at the time of the clinical cut-off or who were lost to follow-up were censored at the date of the last tumor assessment showing no progression of disease either during the study or during follow-up. Participants with no post-baseline assessments were censored at the date of randomization. One participant in the KRAS Mutant FOLFIRI and two participants in KRAS Mutant RO5083945 + FOLFIRI were censored for PFS analysis.
Analysis population: ITT population.

End point type	Primary

End point timeframe:

Randomization up to clinical cutoff (16.1 months)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point reported statistics only on the KRAS mutant participants.

End point values	KRAS Mutant (FOLFIRI)	KRAS Mutant (RO5083945 + FOLFIRI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: months				
median (confidence interval 95%)	4.3 (2.3 to 7.1)	5.2 (3.8 to 5.6)		

Statistical analyses

Statistical analysis title	PFS in KRAS Mutant Participants
Comparison groups	KRAS Mutant (FOLFIRI) v KRAS Mutant (RO5083945 + FOLFIRI)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8104 [4]
Method	Log-Rank, stratified
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.54

Notes:

[4] - The three stratification factors included EGFR expression, time to disease progression on first line treatment, and prior treatment with bevacizumab.

Secondary: Percentage of Participants with a Best Overall Response of Complete Response (CR) or Partial Response (PR) (Objective Response Rate)

End point title	Percentage of Participants with a Best Overall Response of Complete Response (CR) or Partial Response (PR) (Objective Response Rate)

End point description:

Best overall response was assessed by RECIST v 1.1 criteria. Participants without any assessments were regarded as non-responders. CR is the disappearence of target lesions. PR is defined as at least 30 percent (%) decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameter.
Analysis was not performed due to no further clinical development of RO5083945.

End point type	Secondary

End point timeframe:

Baseline, every 8 weeks after Cycle 1 Day 1 until progression, unacceptable toxicity, or withdrawal of consent (until 27.1 months)

End point values	KRAS Wild Type (Cetuximab + FOLFIRI)	KRAS Wild Type (RO5083945 + FOLFIRI)	KRAS Mutant (FOLFIRI)	KRAS Mutant (RO5083945 + FOLFIRI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[5]	0[6]	0[7]	0[8]
Units: percentage of participants				
number (not applicable)				

Notes:

[5] - Analysis was not performed due to no further clinical development of RO5083945

[6] - Analysis was not performed due to no further clinical development of RO5083945

[7] - Analysis was not performed due to no further clinical development of RO5083945

[8] - Analysis was not performed due to no further clinical development of RO5083945

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response was defined as the time from CR or PR was first documented to the first documented disease progression or death, whichever occurs first. Participants who did not progress or died after they have had a confirmed response are censored at the date of their last tumor measurement or last follow-up for progression of disease.
Duration of response was not analyzed due to no further clinical development of RO5083945.

End point type	Secondary

End point timeframe:

Baseline, every 8 weeks after Cycle 1 Day 1 until progression, unacceptable toxicity, or withdrawal of consent (until 27.1 months)

End point values	KRAS Wild Type (Cetuximab + FOLFIRI)	KRAS Wild Type (RO5083945 + FOLFIRI)	KRAS Mutant (FOLFIRI)	KRAS Mutant (RO5083945 + FOLFIRI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[9]	0[10]	0[11]	0[12]
Units: months				
median (confidence interval 95%)	(to)	(to)	(to)	(to)

Notes:

[9] - Analysis was not performed due to no further clinical development of RO5083945

[10] - Analysis was not performed due to no further clinical development of RO5083945

[11] - Analysis was not performed due to no further clinical development of RO5083945

[12] - Analysis was not performed due to no further clinical development of RO5083945

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Best Overall Response of CR or PR or Stable Disease (SD) (Clinical Benefit Rate)

End point title	Percentage of Participants with a Best Overall Response of CR or PR or Stable Disease (SD) (Clinical Benefit Rate)

End point description:

Best overall response was assessed using RECIST v1.1 criteria. Participants without any assessments were regarded as non-responders. CR was the disappearence of target lesions. PR was defined as at least 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameter. PD was at least a 20% increase in the sum of diameter of target lesions, taking as reference the smallest on study including baseline. SD was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Analysis was not performed due to no further clinical development of RO5083945.

End point type	Secondary

End point timeframe:

Baseline, every 8 weeks after Cycle 1 Day 1 until progression, unacceptable toxicity, or withdrawal of consent (until 27.1 months)

End point values	KRAS Wild Type (Cetuximab + FOLFIRI)	KRAS Wild Type (RO5083945 + FOLFIRI)	KRAS Mutant (FOLFIRI)	KRAS Mutant (RO5083945 + FOLFIRI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[13]	0[14]	0[15]	0[16]
Units: percentage of participants				
number (not applicable)				

Notes:

[13] - Analysis was not performed due to no further clinical development of RO5083945

[14] - Analysis was not performed due to no further clinical development of RO5083945

[15] - Analysis was not performed due to no further clinical development of RO5083945

[16] - Analysis was not performed due to no further clinical development of RO5083945

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time between randomization and date of death. Participants without an event were censored at the last date known to be alive. Participants without any follow-up information were censored at the date of randomization.
Overall survival was not analyzed due to no further clinical development of RO5083945.

End point type	Secondary

End point timeframe:

Baseline, every 8 weeks after Cycle 1 Day 1 until progression, unacceptable toxicity, or withdrawal of consent (until 27.1 months)

End point values	KRAS Wild Type (Cetuximab + FOLFIRI)	KRAS Wild Type (RO5083945 + FOLFIRI)	KRAS Mutant (FOLFIRI)	KRAS Mutant (RO5083945 + FOLFIRI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[17]	0[18]	0[19]	0[20]
Units: years				
median (confidence interval 95%)	(to)	(to)	(to)	(to)

Notes:

[17] - Analysis was not performed due to no further clinical development of RO5083945

[18] - Analysis was not performed due to no further clinical development of RO5083945

[19] - Analysis was not performed due to no further clinical development of RO5083945

[20] - Analysis was not performed due to no further clinical development of RO5083945

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Concomitant FOLFIRI on Pharmacokinetics of RO5083945

End point title	Effect of Concomitant FOLFIRI on Pharmacokinetics of RO5083945[21]

End point description:

Pharmacokinetic analysis was not performed due to no further clinical development of RO5083945.

End point type	Secondary

End point timeframe:

RO5083945: Cycle 1, day 8: predose and end of infusion; Cycle 2, 3, and 6, day 1: predose; Cycle 4, day 1: predose and end of infusion; and at safety follow-up visit
FOLFIRI: Cycle 4, day 1

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis of pharmacokinetic parameters was performed on RO5083945 and FOLFIRI alone, and so cetuximab + FOLFIRI group was excluded from analysis.

End point values	KRAS Wild Type (RO5083945 + FOLFIRI)	KRAS Mutant (FOLFIRI)	KRAS Mutant (RO5083945 + FOLFIRI)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[22]	0[23]	0[24]	
Units: nanogram(s)/milliliter				
log mean (standard deviation)	()	()	()	

Notes:

[22] - Analysis was not performed due to no further clinical development of RO5083945

[23] - Analysis was not performed due to no further clinical development of RO5083945

[24] - Analysis was not performed due to no further clinical development of RO5083945

Statistical analyses

No statistical analyses for this end point

Secondary: Relationship Between Immune Effector Cells in Blood and Tumor and Clinical Outcome

End point title	Relationship Between Immune Effector Cells in Blood and Tumor and Clinical Outcome

End point description:

Blood samples were to be analyzed for cytokine exploratory panel, immunophenotyping and human T-regulatory test, and immune functionality assessments.The relationship between immune effector cells (in blood and tumor) versus the clinical outcome parameters (e.g. responders versus non responders, PFS) and stratification factors. The three stratification factors included EGFR expression, time to disease progression on first line treatment and prior treatment with bevacizumab. These analyses were not performed due to no further clinical development of RO5083945.

End point type	Secondary

End point timeframe:

Cycle 1 day 1; Cycle 1 day 8; Cycle 2 day 1 (predose and 24 hours post start of first study medication); Cycle 4 day 1 (predose of first study medication) for every 4 cycles (until 27.1 months)

End point values	KRAS Wild Type (Cetuximab + FOLFIRI)	KRAS Wild Type (RO5083945 + FOLFIRI)	KRAS Mutant (FOLFIRI)	KRAS Mutant (RO5083945 + FOLFIRI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[25]	0[26]	0[27]	0[28]
Units: units on a scale				
number (not applicable)				

Notes:

[25] - Analysis was not performed due to no further clinical development of RO5083945

[26] - Analysis was not performed due to no further clinical development of RO5083945

[27] - Analysis was not performed due to no further clinical development of RO5083945

[28] - Analysis was not performed due to no further clinical development of RO5083945

Statistical analyses

No statistical analyses for this end point

Secondary: Relationship Between EGFR Expression and Clinical Outcome

End point title	Relationship Between EGFR Expression and Clinical Outcome

End point description:

The relationship between EGFR expression versus the clinical outcome parameters (e.g. responders versus non responders, PFS) and stratification factors was assessed. The three stratification factors included EGFR expression, time to disease progression on first line treatment and prior treatment with bevacizumab. Analysis was not performed due to no further clinical development of RO5083945.

End point type	Secondary

End point timeframe:

Randomization up to clinical cutoff (20.9 months)

End point values	KRAS Wild Type (Cetuximab + FOLFIRI)	KRAS Wild Type (RO5083945 + FOLFIRI)	KRAS Mutant (FOLFIRI)	KRAS Mutant (RO5083945 + FOLFIRI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[29]	0[30]	0[31]	0[32]
Units: units on a scale				
log mean (standard deviation)	()	()	()	()

Notes:
[29] - Analysis was not performed due to no further clinical development of RO5083945
[30] - Analysis was not performed due to no further clinical development of RO5083945
[31] - Analysis was not performed due to no further clinical development of RO5083945
[32] - Analysis was not performed due to no further clinical development of RO5083945

Statistical analyses

No statistical analyses for this end point

Secondary: EGFR Expression in Archival and Fresh Tumor Biopsies

End point title	EGFR Expression in Archival and Fresh Tumor Biopsies

End point description:
Analysis was not performed due to no further clinical development of RO5083945.

End point type	Secondary

End point timeframe:
Baseline, Cycle 2, Day 1 and Cycle 3 Day 8

End point values	KRAS Wild Type (Cetuximab + FOLFIRI)	KRAS Wild Type (RO5083945 + FOLFIRI)	KRAS Mutant (FOLFIRI)	KRAS Mutant (RO5083945 + FOLFIRI)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[33]	0[34]	0[35]	0[36]
Units: units on a scale				
log mean (standard deviation)	()	()	()	()

Notes:
[33] - Analysis was not performed due to no further clinical development of RO5083945
[34] - Analysis was not performed due to no further clinical development of RO5083945
[35] - Analysis was not performed due to no further clinical development of RO5083945
[36] - Analysis was not performed due to no further clinical development of RO5083945

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening through end of study (Month 32) including 28-day safety follow-up visit

Adverse event reporting additional description:

Safety population: participants who received at least one dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	KRAS Wild Type (Cetuximab + FOLFIRI)

Reporting group description:

Cetuximab: The first dose of cetuximab was 400 mg/m2 body surface area for 120 minutes on Day 1 of Cycle 1 followed by weekly doses of 250 mg/m2 for 60 minutes as an IV infusion until disease progression, unacceptable toxicity, or withdrawal of consent.
FOLFIRI: FOLFIRI is a combination of irinotecan, 5-FU, and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Reporting group title	KRAS Wild Type (RO5083945 + FOLFIRI)

Reporting group description:

RO5083945: RO5083945 1400 mg administered as an IV infusion on Day 1 of Weeks 1 and 2, then once every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.
FOLFIRI: FOLFIRI is a combination of irinotecan, 5-FU, and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Reporting group title	KRAS Mutant (RO5083945 + FOLFIRI)

Reporting group description:

RO5083945: RO5083945 1400 mg administered as an IV infusion on Day 1 of Weeks 1 and 2, then once every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.
FOLFIRI: FOLFIRI is a combination of irinotecan, 5-FU, and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Reporting group title	KRAS Mutant (FOLFIRI)

Reporting group description:

FOLFIRI is a combination of irinotecan, 5-FU, and folinic acid, which was administered as follows:
Irinotecan (180 mg/m2 over 60 minutes) plus 5-FU (400 mg/m2 bolus), followed by 5-FU 2400 mg/m2, 46-hour continuous infusion plus folinic acid (400 mg/m2 [racemic] or 200 mg/m2 [L-Form] over 120 minutes). FOLFIRI was administered on Day 8 of Cycle 1 and then on Day 1 every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Serious adverse events	KRAS Wild Type (Cetuximab + FOLFIRI)	KRAS Wild Type (RO5083945 + FOLFIRI)	KRAS Mutant (RO5083945 + FOLFIRI)
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 41 (29.27%)	21 / 40 (52.50%)	22 / 44 (50.00%)
number of deaths (all causes)	0	2	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer recurrent			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			

subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 41 (4.88%)	1 / 40 (2.50%)	4 / 44 (9.09%)
occurrences causally related to treatment / all	0 / 2	1 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	3 / 44 (6.82%)
occurrences causally related to treatment / all	0 / 0	2 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Scapula fracture			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	2 / 44 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 41 (2.44%)	3 / 40 (7.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			

subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 41 (4.88%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	2 / 44 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			

subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal perforation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Portal vein thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Groin pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	2 / 41 (4.88%)	1 / 40 (2.50%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	3 / 3	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 41 (2.44%)	2 / 40 (5.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	2 / 44 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 41 (2.44%)	2 / 40 (5.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Abdominal infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	2 / 44 (4.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	2 / 44 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			

subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	2 / 44 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	KRAS Mutant (FOLFIRI)		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 42 (28.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer recurrent			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphoedema			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	2 / 42 (4.76%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Infusion related reaction				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Rib fracture			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Scapula fracture			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				

subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea haemorrhagic				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenal perforation				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				

subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Portal vein thrombosis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Renal failure acute			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Groin pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal infection			

subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic infection				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypocalcaemia				

subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	KRAS Wild Type (Cetuximab + FOLFIRI)	KRAS Wild Type (RO5083945 + FOLFIRI)	KRAS Mutant (RO5083945 + FOLFIRI)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 41 (100.00%)	40 / 40 (100.00%)	43 / 44 (97.73%)
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 41 (2.44%)	1 / 40 (2.50%)	3 / 44 (6.82%)
occurrences (all)	1	1	3
Hypotension			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	1 / 44 (2.27%)
occurrences (all)	0	4	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 41 (43.90%)	16 / 40 (40.00%)	16 / 44 (36.36%)
occurrences (all)	34	20	26
Asthenia			
subjects affected / exposed	14 / 41 (34.15%)	10 / 40 (25.00%)	12 / 44 (27.27%)
occurrences (all)	20	25	32
Pyrexia			
subjects affected / exposed	7 / 41 (17.07%)	11 / 40 (27.50%)	8 / 44 (18.18%)
occurrences (all)	8	21	11
Oedema peripheral			
subjects affected / exposed	4 / 41 (9.76%)	7 / 40 (17.50%)	4 / 44 (9.09%)
occurrences (all)	4	9	4
Chest pain			

subjects affected / exposed	4 / 41 (9.76%)	1 / 40 (2.50%)	3 / 44 (6.82%)
occurrences (all)	5	1	5
Pain			
subjects affected / exposed	2 / 41 (4.88%)	1 / 40 (2.50%)	3 / 44 (6.82%)
occurrences (all)	2	1	3
Local swelling			
subjects affected / exposed	1 / 41 (2.44%)	2 / 40 (5.00%)	3 / 44 (6.82%)
occurrences (all)	1	2	4
Mucosal inflammation			
subjects affected / exposed	3 / 41 (7.32%)	1 / 40 (2.50%)	1 / 44 (2.27%)
occurrences (all)	4	1	1
Chills			
subjects affected / exposed	0 / 41 (0.00%)	3 / 40 (7.50%)	2 / 44 (4.55%)
occurrences (all)	0	5	2
Malaise			
subjects affected / exposed	2 / 41 (4.88%)	2 / 40 (5.00%)	1 / 44 (2.27%)
occurrences (all)	2	2	4
Mucosal hyperaemia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	2 / 44 (4.55%)
occurrences (all)	0	2	2
Thrombosis in device			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	0 / 44 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 41 (14.63%)	8 / 40 (20.00%)	6 / 44 (13.64%)
occurrences (all)	7	9	6
Dyspnoea			
subjects affected / exposed	3 / 41 (7.32%)	5 / 40 (12.50%)	6 / 44 (13.64%)
occurrences (all)	3	5	9
Epistaxis			
subjects affected / exposed	3 / 41 (7.32%)	3 / 40 (7.50%)	7 / 44 (15.91%)
occurrences (all)	3	5	10
Pulmonary embolism			

subjects affected / exposed	2 / 41 (4.88%)	1 / 40 (2.50%)	4 / 44 (9.09%)
occurrences (all)	3	1	5
Oropharyngeal pain			
subjects affected / exposed	2 / 41 (4.88%)	1 / 40 (2.50%)	3 / 44 (6.82%)
occurrences (all)	2	1	3
Dysphonia			
subjects affected / exposed	2 / 41 (4.88%)	2 / 40 (5.00%)	0 / 44 (0.00%)
occurrences (all)	2	3	0
Rhinorrhoea			
subjects affected / exposed	0 / 41 (0.00%)	3 / 40 (7.50%)	1 / 44 (2.27%)
occurrences (all)	0	3	1
Dyspnoea exertional			
subjects affected / exposed	3 / 41 (7.32%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences (all)	4	0	0
Hiccups			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	1 / 44 (2.27%)
occurrences (all)	0	5	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 41 (9.76%)	8 / 40 (20.00%)	2 / 44 (4.55%)
occurrences (all)	4	8	5
Agitation			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	0 / 44 (0.00%)
occurrences (all)	0	2	0
Anxiety			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	3 / 44 (6.82%)
occurrences (all)	0	0	3
Investigations			
Weight decreased			
subjects affected / exposed	4 / 41 (9.76%)	6 / 40 (15.00%)	3 / 44 (6.82%)
occurrences (all)	4	6	3
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	6 / 41 (14.63%)	29 / 40 (72.50%)	35 / 44 (79.55%)
occurrences (all)	6	39	55
Cardiac disorders			

Palpitations			
subjects affected / exposed	4 / 41 (9.76%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences (all)	5	0	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	4 / 41 (9.76%)	7 / 40 (17.50%)	8 / 44 (18.18%)
occurrences (all)	5	7	9
Dizziness			
subjects affected / exposed	2 / 41 (4.88%)	2 / 40 (5.00%)	4 / 44 (9.09%)
occurrences (all)	3	2	5
Lethargy			
subjects affected / exposed	5 / 41 (12.20%)	3 / 40 (7.50%)	5 / 44 (11.36%)
occurrences (all)	6	3	5
Headache			
subjects affected / exposed	6 / 41 (14.63%)	2 / 40 (5.00%)	2 / 44 (4.55%)
occurrences (all)	6	2	2
Neuropathy peripheral			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	3 / 44 (6.82%)
occurrences (all)	1	0	3
Paraesthesia			
subjects affected / exposed	6 / 41 (14.63%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences (all)	6	0	1
Cholinergic syndrome			
subjects affected / exposed	4 / 41 (9.76%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences (all)	4	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 41 (2.44%)	2 / 40 (5.00%)	0 / 44 (0.00%)
occurrences (all)	1	2	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	19 / 41 (46.34%)	16 / 40 (40.00%)	16 / 44 (36.36%)
occurrences (all)	54	44	20
Anaemia			
subjects affected / exposed	7 / 41 (17.07%)	7 / 40 (17.50%)	6 / 44 (13.64%)
occurrences (all)	8	9	9
Thrombocytopenia			

subjects affected / exposed	0 / 41 (0.00%)	4 / 40 (10.00%)	2 / 44 (4.55%)
occurrences (all)	0	4	2
Leukopenia			
subjects affected / exposed	3 / 41 (7.32%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences (all)	4	0	1
Eye disorders			
Conjunctivitis			
subjects affected / exposed	6 / 41 (14.63%)	10 / 40 (25.00%)	6 / 44 (13.64%)
occurrences (all)	9	22	9
Lacrimation increased			
subjects affected / exposed	2 / 41 (4.88%)	2 / 40 (5.00%)	2 / 44 (4.55%)
occurrences (all)	2	5	2
Dry eye			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	3 / 44 (6.82%)
occurrences (all)	0	2	3
Ocular hyperaemia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	1 / 44 (2.27%)
occurrences (all)	0	2	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	30 / 41 (73.17%)	28 / 40 (70.00%)	23 / 44 (52.27%)
occurrences (all)	79	80	58
Nausea			
subjects affected / exposed	16 / 41 (39.02%)	17 / 40 (42.50%)	24 / 44 (54.55%)
occurrences (all)	27	37	48
Stomatitis			
subjects affected / exposed	16 / 41 (39.02%)	12 / 40 (30.00%)	17 / 44 (38.64%)
occurrences (all)	31	21	33
Constipation			
subjects affected / exposed	18 / 41 (43.90%)	8 / 40 (20.00%)	16 / 44 (36.36%)
occurrences (all)	31	9	26
Abdominal pain			
subjects affected / exposed	12 / 41 (29.27%)	11 / 40 (27.50%)	11 / 44 (25.00%)
occurrences (all)	15	20	18
Vomiting			

subjects affected / exposed	11 / 41 (26.83%)	11 / 40 (27.50%)	12 / 44 (27.27%)
occurrences (all)	16	19	29
Abdominal pain upper			
subjects affected / exposed	8 / 41 (19.51%)	6 / 40 (15.00%)	4 / 44 (9.09%)
occurrences (all)	13	6	5
Dyspepsia			
subjects affected / exposed	4 / 41 (9.76%)	0 / 40 (0.00%)	5 / 44 (11.36%)
occurrences (all)	4	0	6
Haemorrhoids			
subjects affected / exposed	3 / 41 (7.32%)	6 / 40 (15.00%)	2 / 44 (4.55%)
occurrences (all)	3	6	2
Mouth ulceration			
subjects affected / exposed	3 / 41 (7.32%)	1 / 40 (2.50%)	3 / 44 (6.82%)
occurrences (all)	3	1	3
Rectal haemorrhage			
subjects affected / exposed	2 / 41 (4.88%)	1 / 40 (2.50%)	3 / 44 (6.82%)
occurrences (all)	2	1	4
Cheilitis			
subjects affected / exposed	3 / 41 (7.32%)	1 / 40 (2.50%)	1 / 44 (2.27%)
occurrences (all)	3	1	1
Dry mouth			
subjects affected / exposed	2 / 41 (4.88%)	3 / 40 (7.50%)	2 / 44 (4.55%)
occurrences (all)	3	4	2
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 41 (4.88%)	2 / 40 (5.00%)	2 / 44 (4.55%)
occurrences (all)	2	2	3
Abdominal distension			
subjects affected / exposed	2 / 41 (4.88%)	0 / 40 (0.00%)	1 / 44 (2.27%)
occurrences (all)	2	0	1
Toothache			
subjects affected / exposed	2 / 41 (4.88%)	2 / 40 (5.00%)	1 / 44 (2.27%)
occurrences (all)	2	2	1
Glossodynia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	1 / 44 (2.27%)
occurrences (all)	0	3	1
Abdominal pain lower			

subjects affected / exposed	1 / 41 (2.44%)	2 / 40 (5.00%)	0 / 44 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 41 (7.32%)	0 / 40 (0.00%)	0 / 44 (0.00%)
occurrences (all)	3	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	29 / 41 (70.73%)	24 / 40 (60.00%)	27 / 44 (61.36%)
occurrences (all)	39	33	29
Dry skin			
subjects affected / exposed	17 / 41 (41.46%)	14 / 40 (35.00%)	10 / 44 (22.73%)
occurrences (all)	20	18	12
Alopecia			
subjects affected / exposed	5 / 41 (12.20%)	9 / 40 (22.50%)	11 / 44 (25.00%)
occurrences (all)	5	9	11
Pruritus			
subjects affected / exposed	7 / 41 (17.07%)	11 / 40 (27.50%)	4 / 44 (9.09%)
occurrences (all)	7	12	4
Dermatitis acneiform			
subjects affected / exposed	8 / 41 (19.51%)	6 / 40 (15.00%)	7 / 44 (15.91%)
occurrences (all)	9	6	12
Skin fissures			
subjects affected / exposed	8 / 41 (19.51%)	7 / 40 (17.50%)	3 / 44 (6.82%)
occurrences (all)	9	8	4
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	6 / 41 (14.63%)	2 / 40 (5.00%)	4 / 44 (9.09%)
occurrences (all)	6	2	5
Acne	Additional description: 4		
subjects affected / exposed	4 / 41 (9.76%)	3 / 40 (7.50%)	3 / 44 (6.82%)
occurrences (all)	6	3	3
Erythema			
subjects affected / exposed	3 / 41 (7.32%)	5 / 40 (12.50%)	1 / 44 (2.27%)
occurrences (all)	3	6	1
Drug eruption			

subjects affected / exposed	3 / 41 (7.32%)	2 / 40 (5.00%)	2 / 44 (4.55%)
occurrences (all)	4	2	2
Hypertrichosis			
subjects affected / exposed	3 / 41 (7.32%)	1 / 40 (2.50%)	3 / 44 (6.82%)
occurrences (all)	3	1	3
Hyperhidrosis			
subjects affected / exposed	0 / 41 (0.00%)	3 / 40 (7.50%)	1 / 44 (2.27%)
occurrences (all)	0	3	1
Skin hyperpigmentation			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	1 / 44 (2.27%)
occurrences (all)	0	2	1
Pain of skin			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	0 / 44 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 41 (2.44%)	2 / 40 (5.00%)	2 / 44 (4.55%)
occurrences (all)	1	2	2
Haematuria			
subjects affected / exposed	0 / 41 (0.00%)	4 / 40 (10.00%)	0 / 44 (0.00%)
occurrences (all)	0	8	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 41 (17.07%)	9 / 40 (22.50%)	12 / 44 (27.27%)
occurrences (all)	9	11	15
Pain in extremity			
subjects affected / exposed	3 / 41 (7.32%)	3 / 40 (7.50%)	3 / 44 (6.82%)
occurrences (all)	4	4	11
Arthralgia			
subjects affected / exposed	2 / 41 (4.88%)	1 / 40 (2.50%)	3 / 44 (6.82%)
occurrences (all)	2	1	3
Musculoskeletal chest pain			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	4 / 44 (9.09%)
occurrences (all)	1	0	4
Myalgia			

subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	2 / 44 (4.55%)
occurrences (all)	0	0	3
Muscle spasms			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	2 / 44 (4.55%)
occurrences (all)	0	2	2
Joint swelling			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	1 / 44 (2.27%)
occurrences (all)	0	2	1
Infections and infestations			
Paronychia			
subjects affected / exposed	18 / 41 (43.90%)	12 / 40 (30.00%)	9 / 44 (20.45%)
occurrences (all)	24	15	11
Nasopharyngitis			
subjects affected / exposed	3 / 41 (7.32%)	4 / 40 (10.00%)	2 / 44 (4.55%)
occurrences (all)	3	4	2
Folliculitis			
subjects affected / exposed	4 / 41 (9.76%)	4 / 40 (10.00%)	2 / 44 (4.55%)
occurrences (all)	6	4	2
Upper respiratory tract infection			
subjects affected / exposed	3 / 41 (7.32%)	2 / 40 (5.00%)	0 / 44 (0.00%)
occurrences (all)	3	2	0
Urinary tract infection			
subjects affected / exposed	2 / 41 (4.88%)	4 / 40 (10.00%)	1 / 44 (2.27%)
occurrences (all)	6	4	1
Infection			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	1 / 44 (2.27%)
occurrences (all)	0	2	1
Influenza			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	1 / 44 (2.27%)
occurrences (all)	0	2	1
Skin infection			
subjects affected / exposed	1 / 41 (2.44%)	2 / 40 (5.00%)	0 / 44 (0.00%)
occurrences (all)	1	3	0
Bronchitis			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	0 / 44 (0.00%)
occurrences (all)	0	2	0

Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	15 / 41 (36.59%)	26 / 40 (65.00%)	25 / 44 (56.82%)
occurrences (all)	20	38	39
Decreased appetite			
subjects affected / exposed	16 / 41 (39.02%)	15 / 40 (37.50%)	17 / 44 (38.64%)
occurrences (all)	17	20	17
Hypokalaemia			
subjects affected / exposed	9 / 41 (21.95%)	10 / 40 (25.00%)	3 / 44 (6.82%)
occurrences (all)	10	18	5
Hypocalcaemia			
subjects affected / exposed	4 / 41 (9.76%)	5 / 40 (12.50%)	4 / 44 (9.09%)
occurrences (all)	4	7	7
Hypophosphataemia			
subjects affected / exposed	2 / 41 (4.88%)	5 / 40 (12.50%)	5 / 44 (11.36%)
occurrences (all)	2	6	5
Dehydration			
subjects affected / exposed	0 / 41 (0.00%)	4 / 40 (10.00%)	2 / 44 (4.55%)
occurrences (all)	0	4	3
Hyperglycaemia			
subjects affected / exposed	4 / 41 (9.76%)	2 / 40 (5.00%)	0 / 44 (0.00%)
occurrences (all)	4	2	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 41 (2.44%)	3 / 40 (7.50%)	0 / 44 (0.00%)
occurrences (all)	1	3	0

Non-serious adverse events	KRAS Mutant (FOLFIRI)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 42 (97.62%)		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
General disorders and administration			

site conditions				
Fatigue				
subjects affected / exposed	15 / 42 (35.71%)			
occurrences (all)	16			
Asthenia				
subjects affected / exposed	17 / 42 (40.48%)			
occurrences (all)	39			
Pyrexia				
subjects affected / exposed	8 / 42 (19.05%)			
occurrences (all)	10			
Oedema peripheral				
subjects affected / exposed	6 / 42 (14.29%)			
occurrences (all)	8			
Chest pain				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Pain				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Local swelling				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Mucosal inflammation				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Chills				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Malaise				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Mucosal hyperaemia				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Thrombosis in device				

subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	5		
Pulmonary embolism			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Dysphonia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Dyspnoea exertional			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Hiccups			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Agitation			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Investigations			
Weight decreased			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	6		
Dizziness			
subjects affected / exposed	6 / 42 (14.29%)		
occurrences (all)	6		
Lethargy			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Neuropathy peripheral			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Paraesthesia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		

Cholinergic syndrome subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1 0 / 42 (0.00%) 0		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all)	 15 / 42 (35.71%) 27 15 / 42 (35.71%) 16 2 / 42 (4.76%) 3 1 / 42 (2.38%) 2		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all) Lacrimation increased subjects affected / exposed occurrences (all) Dry eye subjects affected / exposed occurrences (all) Ocular hyperaemia subjects affected / exposed occurrences (all)	 2 / 42 (4.76%) 2 0 / 42 (0.00%) 0 0 / 42 (0.00%) 0 0 / 42 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea	 25 / 42 (59.52%) 70 		

subjects affected / exposed	24 / 42 (57.14%)			
occurrences (all)	50			
Stomatitis				
subjects affected / exposed	14 / 42 (33.33%)			
occurrences (all)	35			
Constipation				
subjects affected / exposed	13 / 42 (30.95%)			
occurrences (all)	20			
Abdominal pain				
subjects affected / exposed	9 / 42 (21.43%)			
occurrences (all)	11			
Vomiting				
subjects affected / exposed	8 / 42 (19.05%)			
occurrences (all)	12			
Abdominal pain upper				
subjects affected / exposed	5 / 42 (11.90%)			
occurrences (all)	7			
Dyspepsia				
subjects affected / exposed	4 / 42 (9.52%)			
occurrences (all)	4			
Haemorrhoids				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Mouth ulceration				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Rectal haemorrhage				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences (all)	5			
Cheilitis				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences (all)	2			
Dry mouth				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Gastrooesophageal reflux disease				

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Abdominal distension			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Toothache			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Glossodynia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Abdominal pain lower			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	11 / 42 (26.19%)		
occurrences (all)	14		
Pruritus			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Dermatitis acneiform			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Skin fissures			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		

Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Acne	Additional description: 4		
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Drug eruption			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Hypertrichosis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Skin hyperpigmentation			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Pain of skin			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Haematuria			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Pain in extremity			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Arthralgia			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Muscle spasms			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Joint swelling			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Paronychia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	5		
Folliculitis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		

Influenza subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Skin infection subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Bronchitis subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Metabolism and nutrition disorders Hypomagnesaemia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3		
Decreased appetite subjects affected / exposed occurrences (all)	10 / 42 (23.81%) 12		
Hypokalaemia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3		
Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Hypophosphataemia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Dehydration subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2010	Incorporated editorial changes, addition or deletion of certain text.
16 December 2011	A new section and appendix was added for management of hypomagnesemia. Blood volume estimations were clarified and an additional column of safety blood tests, optional immune functional tests and total blood volumes were updated. Replacement policy was revised to ensure that the primary objective (PFS) was assessed using RECIST 1.1 criteria. Total calcium was changed to calcium ions and corresponding values were added in biochemistry testing. Carcinoembryonic antigen sample collection and urinalysis scheduling was updated in respective sections. The definition of KRAS WT and KRAS mutant treatment groups were revised to align with ICF and electronic CRF (eCRF). Clarified exclusion criterion 08, excluded treatments, scheduling of tumor assessment, baseline assessments for FOLFIRI alone participants (pts), study treatment start of FOLFIRI alone pts, and schedule of assessments. Safety follow-up visit was revised to add information about survival follow-up. Clarified that the screening procedures were required to performed before enrollment and baseline sampling was done after enrolment, because these samples were taken from pts included in the study (i.e. excluding screen failures). Changes made in the ICF that multiple cores/passes were taken during the fresh tumor biopsy to increase the chance of successfully targeting the lesion. Changes made in the ICF that the pt was to be contacted for survival follow-up even after withdrawal from the study.Urine analysis was added to ICF for procedures during treatment. Cetuximab was added as investigational medicinal product in addition with RO5083945. Added a +/- 3 day visit window to allow more flexiblity for scheduling visits during treatment. Subgroup analysis was added to the efficacy analysis. Elevation in aspartate aminotransferase and alanine aminotransferase levels were added in laboratory liver parameters.
30 November 2012	Updated the phase II study BP22349 in non-squamous non-small cell liver carcinoma analysis to present the benefit/risk of RO5083945 in the former indication. Extended collection of overall survival data and modified the definition for end of study. Clarified on the usage of corticosteroids for prophylactic and reactive treatment for rash. Collection of additional subsequent therapies during survival follow-up after the end of study treatment to detect any imbalance across treatment arms.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Secondary efficacy analyses such as overall response, duration of response, clinical benefit rate, overall survival, PK and PD analysis were not performed due to no further clinical development of RO5083945.

Notes: